

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID:SSSPTA1600RXA

PASSWORD:

TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * Welcome to STN International * * * * *

NEWS	1		Web Page URLs for STN Seminar Schedule - N. America
NEWS	2		"Ask CAS" for self-help around the clock
NEWS	3	SEP 01	New pricing for the Save Answers for SciFinder Wizard within STN Express with Discover!
NEWS	4	OCT 28	KOREAPAT now available on STN
NEWS	5	NOV 30	PHAR reloaded with additional data
NEWS	6	DEC 01	LISA now available on STN
NEWS	7	DEC 09	12 databases to be removed from STN on December 31, 2004
NEWS	8	DEC 15	MEDLINE update schedule for December 2004
NEWS	9	DEC 17	ELCOM reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	10	DEC 17	COMPUAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	11	DEC 17	SOLIDSTATE reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	12	DEC 17	CERAB reloaded; updating to resume; current-awareness alerts (SDIs) affected
NEWS	13	DEC 17	THREE NEW FIELDS ADDED TO IFIPAT/IFIUDB/IFICDB
NEWS	14	DEC 30	EPFULL: New patent full text database to be available on STN
NEWS	15	DEC 30	CAPLUS - PATENT COVERAGE EXPANDED
NEWS	16	JAN 03	No connect-hour charges in EPFULL during January and February 2005
NEWS	17	FEB 25	CA/CAPLUS - Russian Agency for Patents and Trademarks (ROSPATENT) added to list of core patent offices covered
NEWS	18	FEB 10	STN Patent Forums to be held in March 2005
NEWS	19	FEB 16	STN User Update to be held in conjunction with the 229th ACS National Meeting on March 13, 2005
NEWS	20	FEB 28	PATDPAFULL - New display fields provide for legal status data from INPADO
NEWS	21	FEB 28	BABS - Current-awareness alerts (SDIs) available
NEWS	22	FEB 28	MEDLINE/LMEDLINE reloaded
NEWS	23	MAR 02	GBFULL: New full-text patent database on STN
NEWS	24	MAR 03	REGISTRY/ZREGISTRY - Sequence annotations enhanced
NEWS	25	MAR 03	MEDLINE file segment of TOXCENTER reloaded
NEWS EXPRESS			JANUARY 10 CURRENT WINDOWS VERSION IS V7.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 10 JANUARY 2005
NEWS HOURS			STN Operating Hours Plus Help Desk Availability
NEWS INTER			General Internet Information
NEWS LOGIN			Welcome Banner and News Items
NEWS PHONE			Direct Dial and Telecommunication Network Access to STN
NEWS WWW			CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

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* * * * * STN Columbus * * * * *

FILE 'HOME' ENTERED AT 06:20:39 ON 18 MAR 2005

=> fil reg

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

0.21

0.21

FILE 'REGISTRY' ENTERED AT 06:20:48 ON 18 MAR 2005

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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 16 MAR 2005 HIGHEST RN 845774-58-5

DICTIONARY FILE UPDATES: 16 MAR 2005 HIGHEST RN 845774-58-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

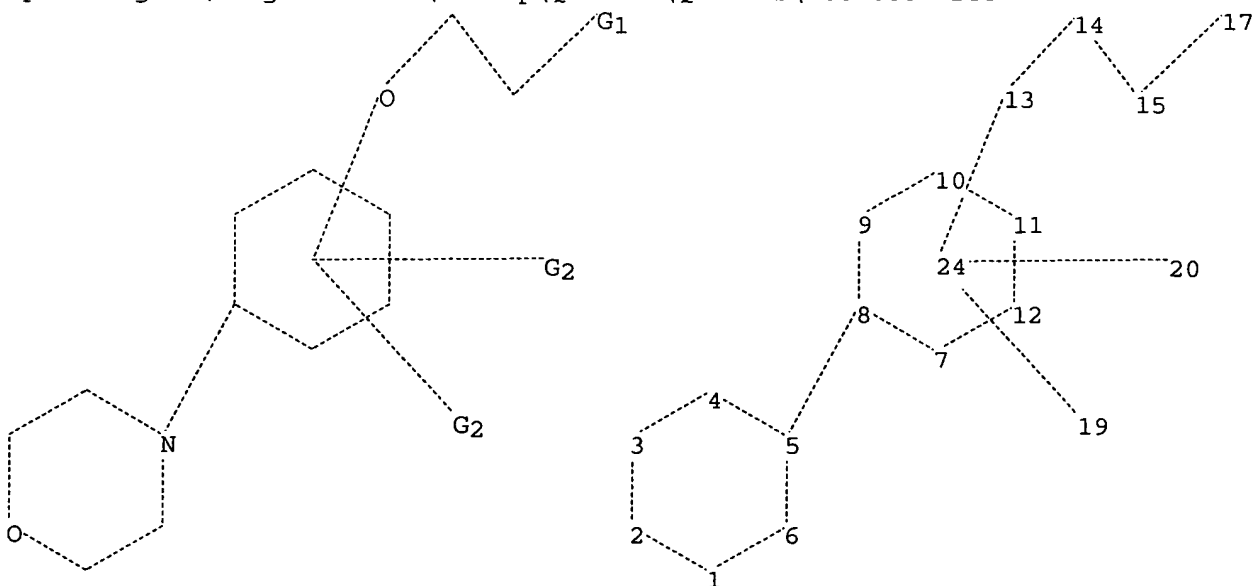
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=>

Uploading C:\Program Files\Stnexp\Queries\QUERIES\10674684.str



chain nodes :

13 14 15 17 19 20

```

ring nodes :
1  2  3  4  5  6  7  8  9  10  11  12
chain bonds :
5-8 13-14 14-15 15-17
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-8 7-8 7-12 8-9 9-10 10-11 11-12 13-14 14-15
15-17
isolated ring systems :
containing 1 : 7 :

```

G1:C,O,S

G2:C,H,O

```

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 17:CLASS 19:CLASS 20:CLASS
22:CLASS 23:CLASS 24:CLASS

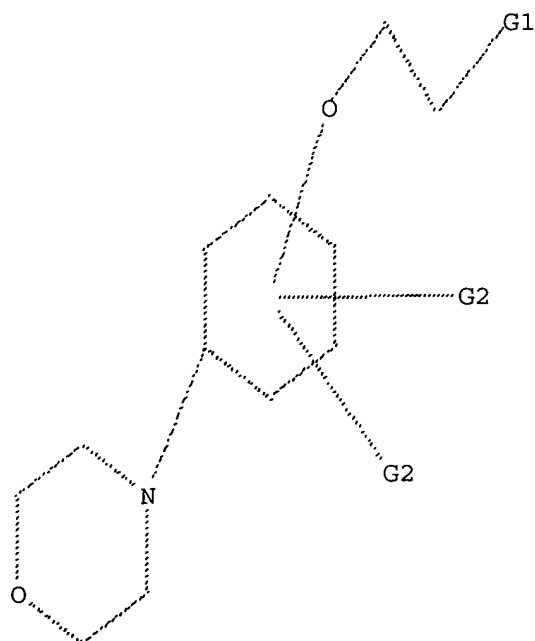
```

L1 STRUCTURE UPLOADED

=> d

L1 HAS NO ANSWERS

L1 STR



G1 C,O,S

G2 C,H,O

Structure attributes must be viewed using STN Express query preparation.

=> s l1

SAMPLE SEARCH INITIATED 06:21:22 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 939 TO ITERATE

100.0% PROCESSED 939 ITERATIONS
SEARCH TIME: 00.00.01

26 ANSWERS

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 16942 TO 20618
PROJECTED ANSWERS: 215 TO 825

L2 26 SEA SSS SAM L1

=> s l1 full
FULL SEARCH INITIATED 06:21:25 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 18870 TO ITERATE

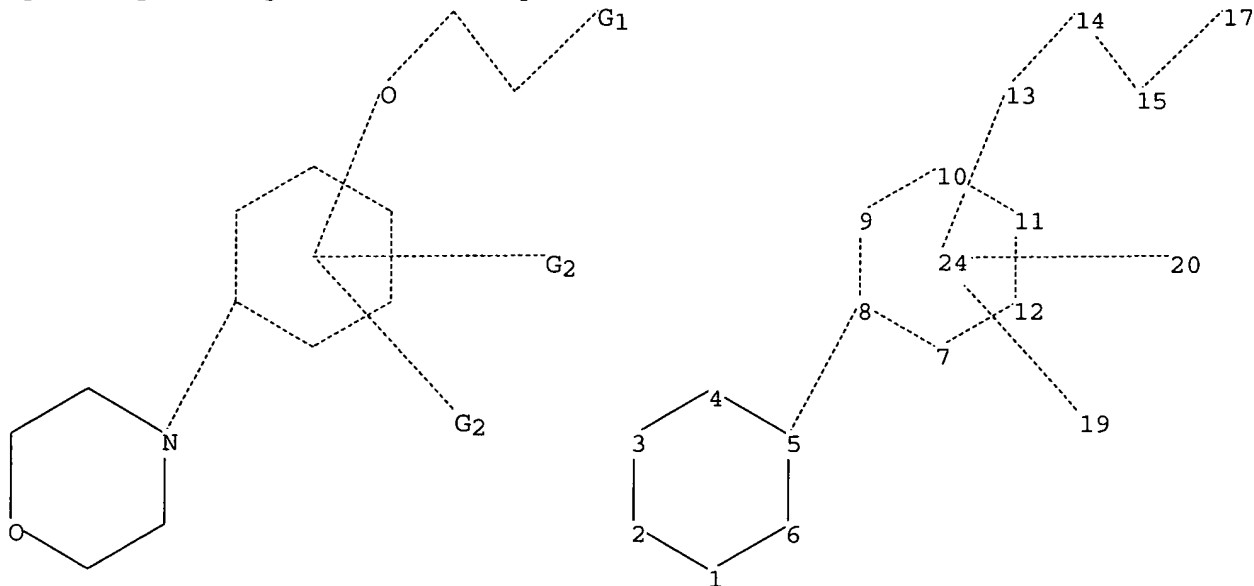
100.0% PROCESSED 18870 ITERATIONS
SEARCH TIME: 00.00.01

520 ANSWERS

L3 520 SEA SSS FUL L1

=> s l3 and caplus/lc
45042485 CAPLUS/LC
L4 405 L3 AND CAPLUS/LC

=>
Uploading C:\Program Files\Stnexp\Queries\QUERIES\106746841.str



chain nodes :

13 14 15 17 19 20

ring nodes :

1 2 3 4 5 6 7 8 9 10 11 12

chain bonds :

5-8 13-14 14-15 15-17

ring bonds :

1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12

exact/norm bonds :

1-2 1-6 2-3 3-4 4-5 5-6 5-8 7-8 7-12 8-9 9-10 10-11 11-12 13-14 14-15
15-17

isolated ring systems :

containing 1 : 7 :

G1:C,O,S

G2:C,H,O

Match level :

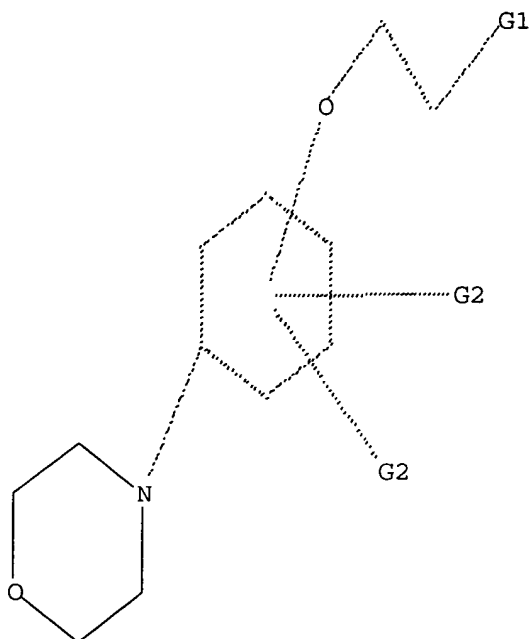
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 17:CLASS 19:CLASS 20:CLASS
22:CLASS 23:CLASS 24:CLASS

L5 STRUCTURE UPLOADED

=> d

L5 HAS NO ANSWERS

L5 STR



G1 C,O,S

G2 C,H,O

Structure attributes must be viewed using STN Express query preparation.

=> s l5 subset=l3 full

FULL SUBSET SEARCH INITIATED 06:22:31 FILE 'REGISTRY'

FULL SUBSET SCREEN SEARCH COMPLETED - 520 TO ITERATE

100.0% PROCESSED 520 ITERATIONS

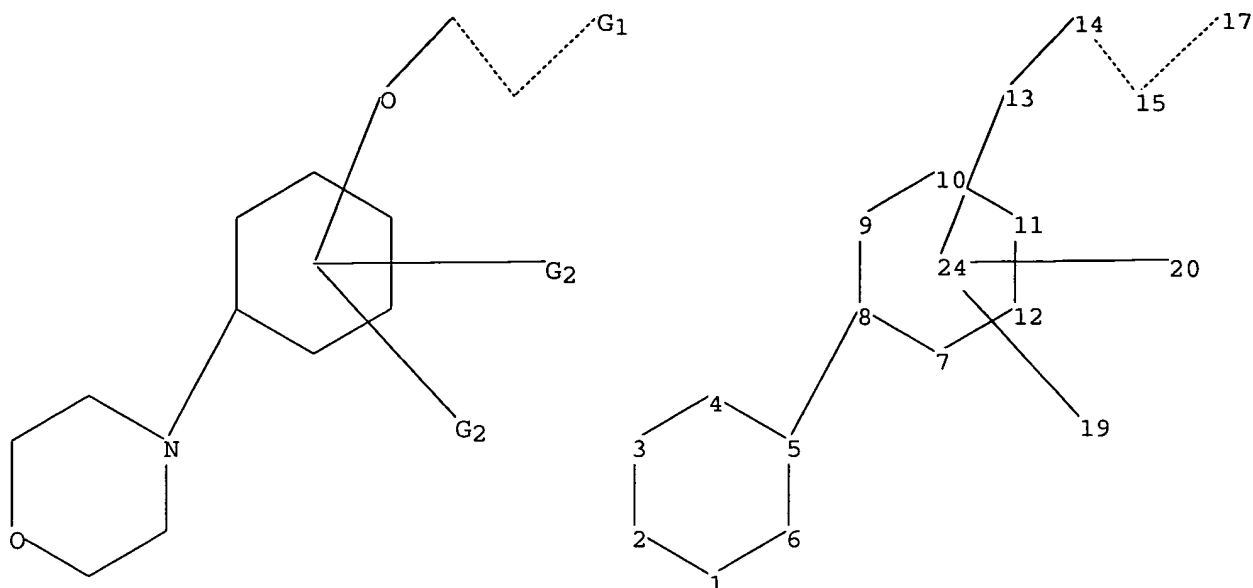
515 ANSWERS

SEARCH TIME: 00.00.01

L6 515 SEA SUB=L3 SSS FUL L5

=>

Uploading C:\Program Files\Stnexp\Queries\QUERIES\106746842.str



```

chain nodes :
13 14 15 17 19 20
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
chain bonds :
5-8 13-14 14-15 15-17
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
1-2 1-6 2-3 3-4 4-5 5-6 5-8 13-14 14-15 15-17
exact bonds :
7-8 7-12 8-9 9-10 10-11 11-12
isolated ring systems :
containing 1 : 7 :

```

G1:C,O,S

G2:C,H,O

Match level :

```

1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 17:CLASS 19:CLASS 20:CLASS
22:CLASS 23:CLASS 24:CLASS

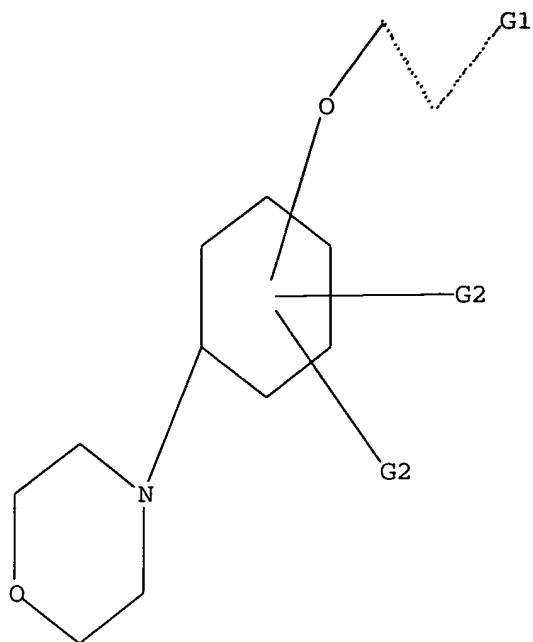
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L7 STRUCTURE UPLOADED

=> d

L7 HAS NO ANSWERS

L7 STR



G1 C,O,S

G2 C,H,O

Structure attributes must be viewed using STN Express query preparation.

=> s l7 subset=l6 full

FULL SUBSET SEARCH INITIATED 06:24:13 FILE 'REGISTRY'

FULL SUBSET SCREEN SEARCH COMPLETED - 31 TO ITERATE

100.0% PROCESSED 31 ITERATIONS

22 ANSWERS

SEARCH TIME: 00.00.01

L8 22 SEA SUB=L6 SSS FUL L7

=> s l8 and caplus/lc

45042485 CAPLUS/LC

L9 21 L8 AND CAPLUS/LC

=> s l8 not l9

L10 1 L8 NOT L9

=> d

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN

RN 807313-63-9 REGISTRY

CN Morpholine, 4-[(1R,2R)-2-[4-(3,4-dimethoxyphenyl)butoxy]cyclohexyl]-, rel-(9CI) (CA INDEX NAME)

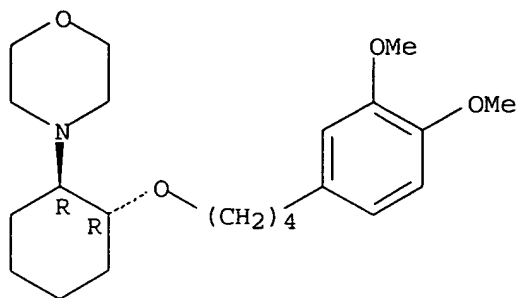
FS STEREOSEARCH

MF C22 H35 N O4

CI COM

SR CA

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

=> d ed l10

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
ED Entered STN: 03 Jan 2005

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	252.89	253.10

FILE 'CAPLUS' ENTERED AT 06:24:57 ON 18 MAR 2005
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FILE COVERS 1907 - 18 Mar 2005 VOL 142 ISS 12
FILE LAST UPDATED: 16 Mar 2005 (20050316/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l9

L11 6 L9

=> d ibib abs hitstr l11 1-6

L11 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:996122 CAPLUS
DOCUMENT NUMBER: 141:424107
TITLE: Preparation of 1-[2-(2-phenylethoxy)cyclohexyl]pyrrolidinol derivatives for treatment of arrhythmia
INVENTOR(S): Beatch, Gregory N.; Choi, Lewis Siu Leung; Jung, Grace; Liu, Yuzhong; Plouvier, Bertrand; Wall,

Richard; Zhu, Jeff; Zolotoy, Alexander; Barrett,
Anthony G. M.

PATENT ASSIGNEE(S): Cardiome Pharma Corp., Can.

SOURCE: PCT Int. Appl., 381 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

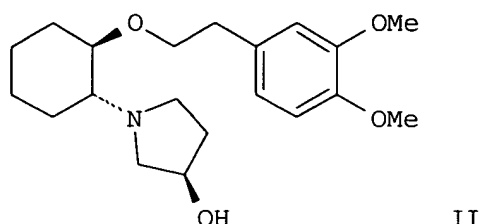
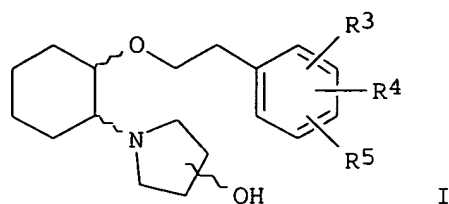
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004099137	A1	20041118	WO 2003-US34655	20031031
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
US 2005038256	A1	20050217	US 2004-862157	20040604
WO 2005016242	A2	20050224	WO 2004-US18050	20040604
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			

PRIORITY APPLN. INFO.:

US 2003-467159P	P	20030502
US 2003-476083P	P	20030604
US 2003-475884P	P	20030605
US 2003-475912P	P	20030605
US 2003-476447P	P	20030605
US 2003-489659P	P	20030723
US 2003-493392P	P	20030807
US 2003-516486P	P	20031031

OTHER SOURCE(S): MARPAT 141:424107

GI



AB Title compds. I [wherein R3-R5 = independently H, OH, alkoxy; with the proviso that R3-R5 cannot all be H; or pharmaceutically acceptable salts, esters, amides, complexes, chelates, stereoisomers, stereoisomeric mixts., geometric isomers, crystalline or amorphous forms, metabolites, metabolic precursors, and prodrugs thereof] were prepared for the treatment of arrhythmia. Compds. of the invention may be also incorporated in compns. and kits. For example, (1R,2R)/(1S,2S)-1-[(3R)-benzyloxypyrrolidinyl]cyclohexan-2-ol (preparation given) was converted to the mesylate and then treated with the alkoxide produced by reaction of 3,4-dimethoxyphenethyl alc. with NaH to afford the ether (70%). Resolution of the diastereomeric mixture, followed by deprotection using Pd/C in 37% HCl provided II•HCl. X-ray structure determination confirmed the absolute configuration and structural assignment. In cardiovascular assays in rats, the II•HCl reduced the arrhythmia score in treated animals to 50% of that shown by control animals at an infusion rate of 1.4 μmol/kg/min and demonstrated low CNS toxicity with a therapeutic index of 18.1.

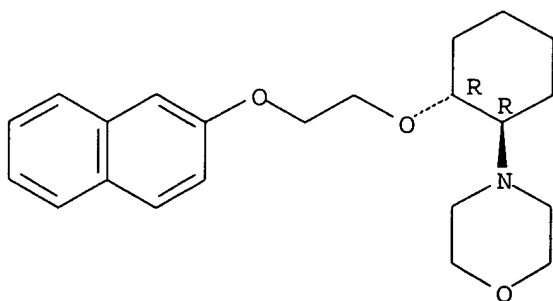
IT **244762-67-2P**, (1R*,2R*)-2-(4-Morpholinyl)-1-[2-(2-naphthoxy)ethoxy]cyclohexane **244762-69-4P** **244762-82-1P** **795282-14-3P**

RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antiarrhythmic; preparation of [(phenylethoxy)cyclohexyl]pyrrolidinol derivs. for treatment of arrhythmia)

RN 244762-67-2 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-(9CI) (CA INDEX NAME)

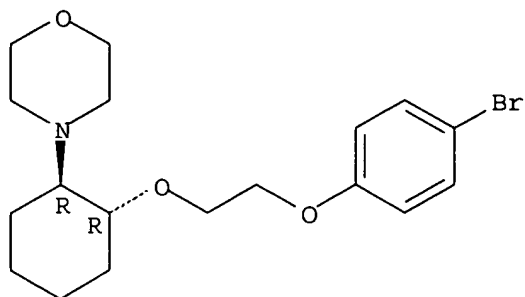
Relative stereochemistry.



RN 244762-69-4 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(9CI) (CA INDEX NAME)

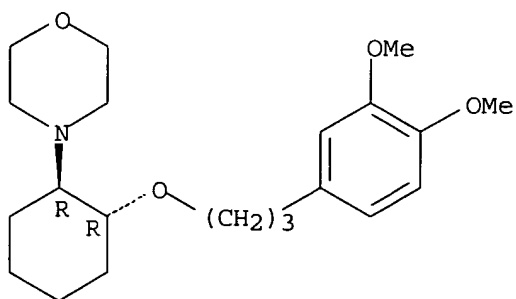
Relative stereochemistry.



RN 244762-82-1 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, hydrochloride, rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

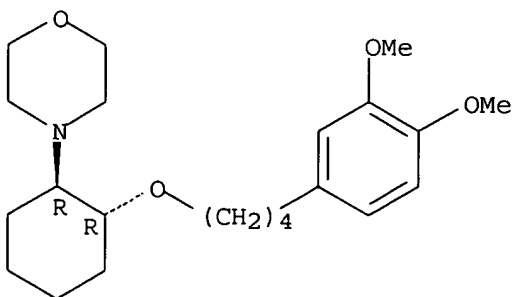


● HCl

RN 795282-14-3 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[4-(3,4-dimethoxyphenyl)butoxy]cyclohexyl]-, hydrochloride, rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.



● HCl

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 2004:396011 CAPLUS

DOCUMENT NUMBER: 141:190792

TITLE: Preparation of aminocyclohexyl ethers as ion channel modulating compounds

INVENTOR(S): Bain, Allen I.; Longley, Cindy J.; Beatch, Gregory N.; Sheng, Tao; Walker, Michael J. A.; Wall, Richard A.; Plouvier, Bertrand M. C.; Zhu, Jiqun; Zolotoy, Alexander B.; Yong, Sandro L.

PATENT ASSIGNEE(S): Nortran Pharmaceuticals Inc., Can.

SOURCE: Can. Pat. Appl., 158 pp.

CODEN: CPXXEB

DOCUMENT TYPE: Patent

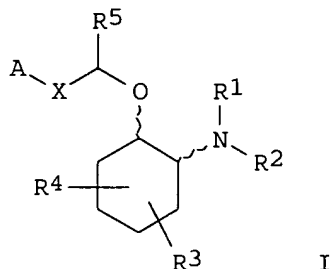
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2268590	AA	20001012	CA 2000-2268590	19990412
PRIORITY APPLN. INFO.:			CA 2000-2268590	19990412
OTHER SOURCE(S):	MARPAT	141:190792		

GI



AB The title amines [I; R1, R2 = H, alkyl, alkoxyalkyl, etc.; NR1R2 = ring such as morpholino, 3-azabicyclo[3.2.2]nonane, etc.; R3, R4 = H, OH, alkyl, alkoxy; or when R3 and R4 are attached to the same ring atom, may together form a spiro 5-6 membered heterocyclic ring; X = a bond, alkenylene, etc.; A = hydrophobic moiety such as Ph, naphthyl, indenyl, etc.; R5 = H, alkyl, aryl, CH2Ph], useful as ion channel modulating compds. were prepared E.g., a multi-step synthesis of (±)-trans-[2-(4-morpholinyl)-1-(2-naphth-2-ylethoxy)]cyclohexane.HCl, starting from morpholine and cyclohexene oxide, was given. The compds. I were tested in various tests (biol. data given). The compds. I may be incorporated in compns. and kits. The present invention also discloses a variety of in vitro and in vivo uses for the compds. I and compns., including the treatment of arrhythmia and the production of analgesia and local anesthesia.

IT 244762-66-1P 244762-67-2P 244762-68-3P
244762-69-4P 244762-82-1P 244763-07-3P
244763-08-4P 244763-09-5P 244763-10-8P
244763-23-3P 244763-24-4P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

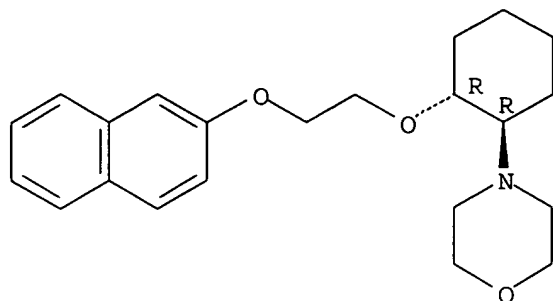
(preparation of aminocyclohexyl ethers as ion channel modulators)

RN 244762-66-1 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-,

hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

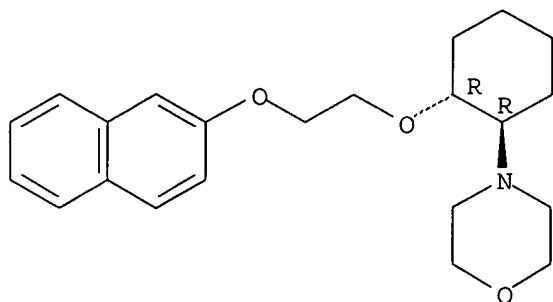


● HCl

RN 244762-67-2 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel- (9CI) (CA INDEX NAME)

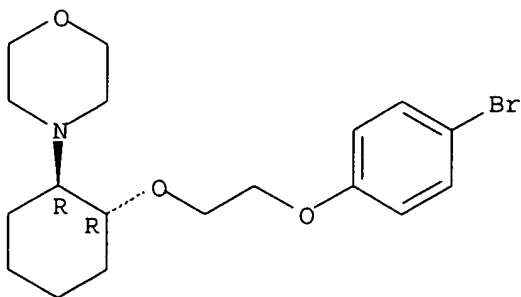
Relative stereochemistry.



RN 244762-68-3 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

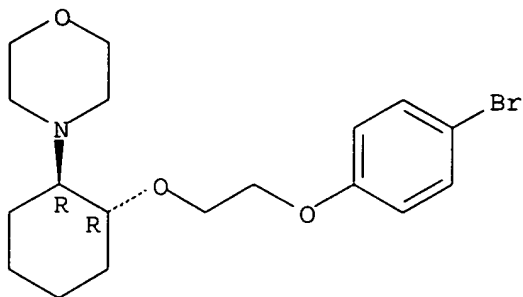


● HCl

RN 244762-69-4 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(9CI) (CA INDEX NAME)

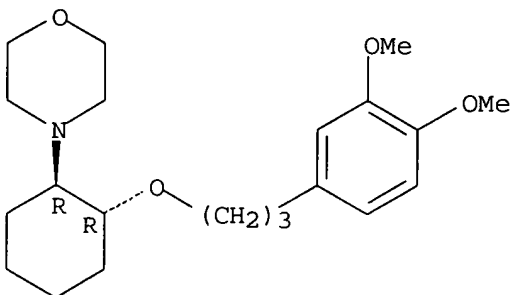
Relative stereochemistry.



RN 244762-82-1 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, hydrochloride, rel-(9CI) (CA INDEX NAME)

Relative stereochemistry.

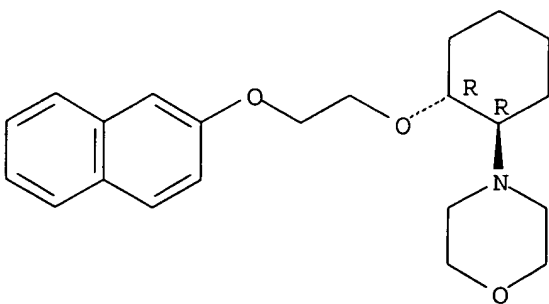


● HCl

RN 244763-07-3 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-(+)-(9CI) (CA INDEX NAME)

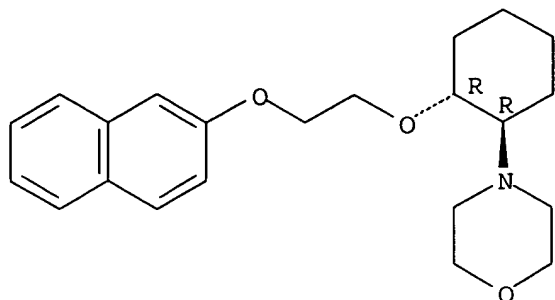
Rotation (+). Absolute stereochemistry unknown.



RN 244763-08-4 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-(-)-(9CI) (CA INDEX NAME)

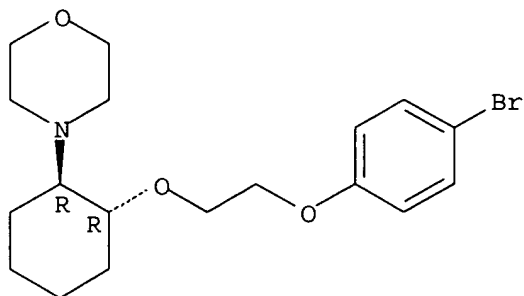
Rotation (-). Absolute stereochemistry unknown.



RN 244763-09-5 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(+)-(9CI) (CA INDEX NAME)

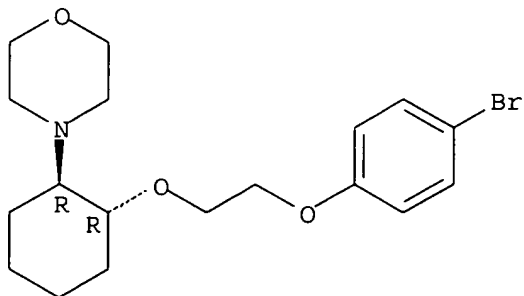
Rotation (+). Absolute stereochemistry unknown.



RN 244763-10-8 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(-)-(9CI) (CA INDEX NAME)

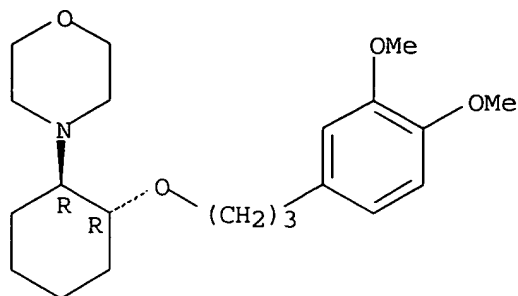
Rotation (-). Absolute stereochemistry unknown.



RN 244763-23-3 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel-(+)-(9CI) (CA INDEX NAME)

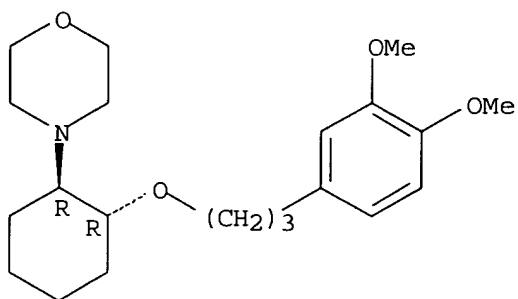
Rotation (+). Absolute stereochemistry unknown.



RN 244763-24-4 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel-(-)-(9CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.



L11 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1999:640819 CAPLUS

DOCUMENT NUMBER: 131:257571

TITLE: Preparation of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents

INVENTOR(S): Bain, Allen I.; Beatch, Gregory N.; Longley, Cindy J.; Plouvier, Bertrand M. C.; Sheng, Tao; Walker, Michael J. A.; Wall, Richard A.; Yong, Sandro L.; Zhu, Jiqun; Zolotoy, Alexander B.

PATENT ASSIGNEE(S): Nortran Pharmaceuticals Inc., Can.

SOURCE: PCT Int. Appl., 141 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

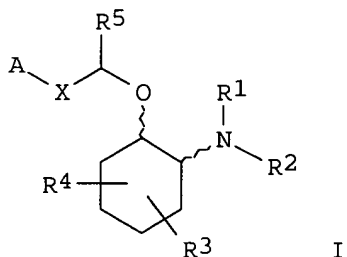
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9950225	A1	19991007	WO 1999-CA280	19990401
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2326777	AA	19991007	CA 1999-2326777	19990401
AU 9930215	A1	19991018	AU 1999-30215	19990401
AU 751772	B2	20020829		

TR 200002796	T2	20001221	TR 2000-200002796	19990401
EP 1087934	A1	20010404	EP 1999-911550	19990401
EP 1087934	B1	20040225		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, LT, LV, FI				
BR 9909282	A	20011016	BR 1999-9282	19990401
EE 200000583	A	20020215	EE 2000-583	19990401
JP 2002509908	T2	20020402	JP 2000-541135	19990401
NZ 507169	A	20040227	NZ 1999-507169	19990401
AT 260240	E	20040315	AT 1999-911550	19990401
EP 1422217	A2	20040526	EP 2004-2165	19990401
EP 1422217	A3	20040616		
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PT 1087934	T	20040730	PT 1999-911550	19990401
ES 2217742	T3	20041101	ES 1999-911550	19990401
ZA 2000005195	A	20020627	ZA 2000-5195	20000927
NO 2000004897	A	20001113	NO 2000-4897	20000929
US 2005020481	A1	20050127	US 2003-674684	20030929
PRIORITY APPLN. INFO.:			US 1998-80347P	P 19980401
			US 1999-118954P	P 19990205
			US 1999-283873	B2 19990331
			EP 1999-911550	A3 19990401
			WO 1999-CA280	W 19990401
			US 2000-680988	B1 20001006
OTHER SOURCE(S):		MARPAT 131:257571		
GI				



AB RZCHR5OZ1NR1R2 [R = (cyclo)alkyl, (un)substituted Ph, -naphthyl, etc.; R1,R2 = H, (ar)alkyl, alkoxyalkyl, hydroxyalkyl; NR1R2 = heterocyclyl; R5 = H, alkyl, CH2Ph, aryl; Z = bond, (un)substituted alkylene, -CH2O, -CH:CH, etc.; Z1 = (un)substituted 1,2-cyclohexylene] were prepared as cardiac Na channel blockers. Thus, cyclohexene oxide was aminated by morpholine and the O-mesylated product etherified by 2-naphthaleneethanol to give title compound trans-I.

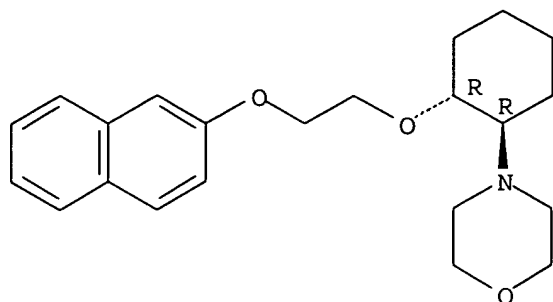
IT 244762-66-1P 244762-67-2P 244762-68-3P
 244762-69-4P 244762-82-1P 244762-83-2P
 244763-07-3P 244763-08-4P 244763-09-5P
 244763-10-8P 244763-23-3P 244763-24-4P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of aralkyl morpholinocyclohexyl ethers and analogs as antiarrhythmic agents)

RN 244762-66-1 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

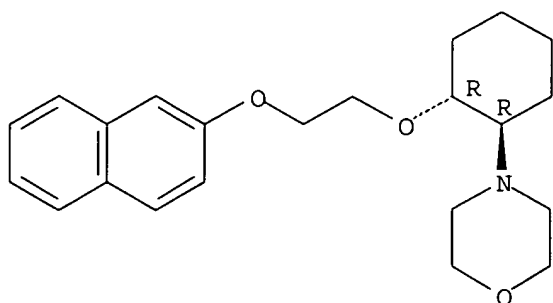
Relative stereochemistry.



● HCl

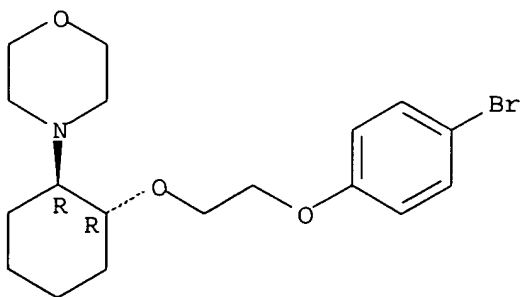
RN 244762-67-2 CAPLUS
 CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-
 (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 244762-68-3 CAPLUS
 CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-,
 hydrochloride, rel- (9CI) (CA INDEX NAME)

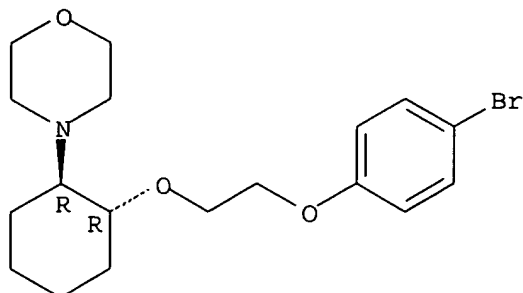
Relative stereochemistry.



● HCl

RN 244762-69-4 CAPLUS
 CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-
 (9CI) (CA INDEX NAME)

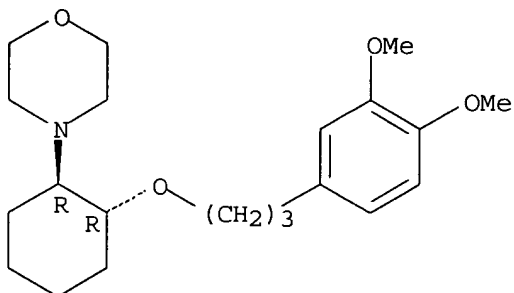
Relative stereochemistry.



RN 244762-82-1 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

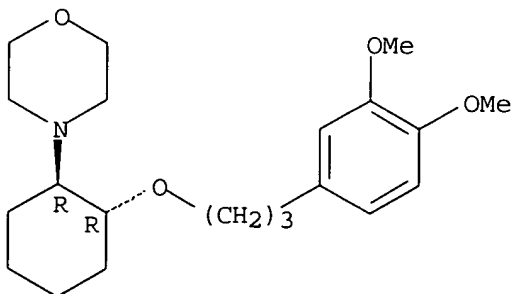


● HCl

RN 244762-83-2 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel- (9CI) (CA INDEX NAME)

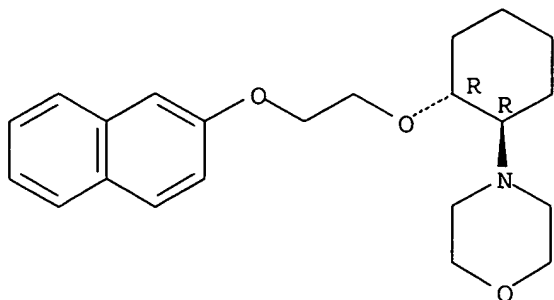
Relative stereochemistry.



RN 244763-07-3 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-(+)- (9CI) (CA INDEX NAME)

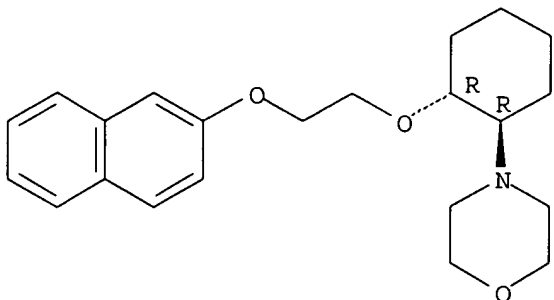
Rotation (+). Absolute stereochemistry unknown.



RN 244763-08-4 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(2-naphthalenyloxy)ethoxy]cyclohexyl]-, rel-(-)-(9CI) (CA INDEX NAME)

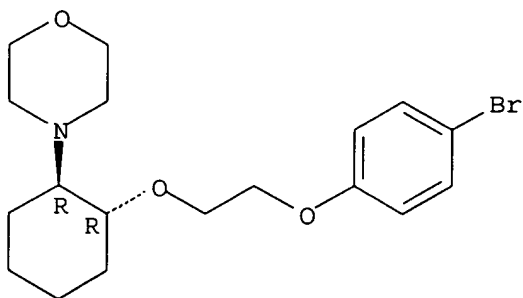
Rotation (-). Absolute stereochemistry unknown.



RN 244763-09-5 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(+)-(9CI) (CA INDEX NAME)

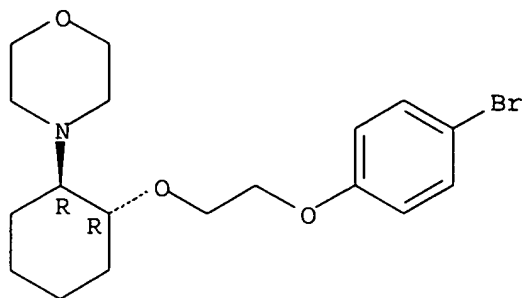
Rotation (+). Absolute stereochemistry unknown.



RN 244763-10-8 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[2-(4-bromophenoxy)ethoxy]cyclohexyl]-, rel-(-)-(9CI) (CA INDEX NAME)

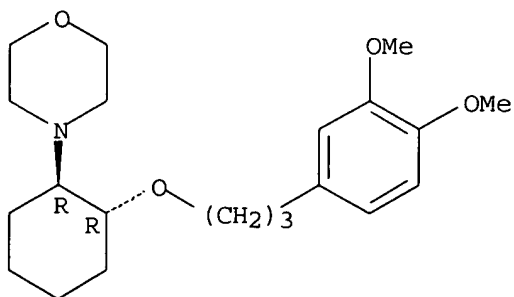
Rotation (-). Absolute stereochemistry unknown.



RN 244763-23-3 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel-(+)- (9CI) (CA INDEX NAME)

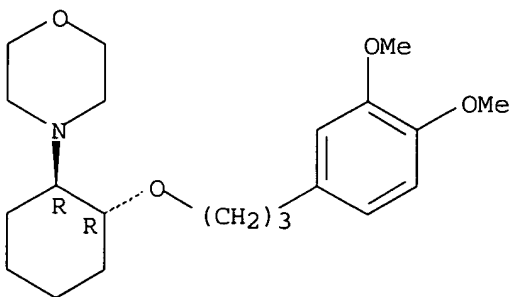
Rotation (+). Absolute stereochemistry unknown.



RN 244763-24-4 CAPLUS

CN Morpholine, 4-[(1R,2R)-2-[3-(3,4-dimethoxyphenyl)propoxy]cyclohexyl]-, rel-(-)- (9CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1997:400459 CAPLUS

DOCUMENT NUMBER: 127:108837

TITLE: Preparation of 2-heterocyclylcyclohexyl esters as antiarrhythmics.

INVENTOR(S): MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.

PATENT ASSIGNEE(S): University of British Columbia, Can.

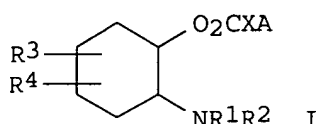
SOURCE: U.S., 25 pp., Cont.-in-part of U.S. Ser. No. 126,575, abandoned.

CODEN: USXXAM

DOCUMENT TYPE: Patent

LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5637583	A	19970610	US 1994-313691	19940927
CA 2172513	AA	19950330	CA 1994-2172513	19940923
ES 2170102	T3	20020801	ES 1994-926755	19940923
US 5885984	A	19990323	US 1997-807728	19970227
US 6174879	B1	20010116	US 1999-271087	19990317
PRIORITY APPLN. INFO.:			US 1993-126575	B2 19930924
			US 1994-313691	A3 19940927
			US 1997-807728	A3 19970227
OTHER SOURCE(S):		MARPAT 127:108837		
GI				



AB Title compds. [I; X = bond, (CH₂)_nY (n = 1, 2, 3; Y = bond, O, S), CH(R₁₂)Y (R₁₂ = alkyl, saturated carbocyclyl, Ph, PhCH₂), C(R₁₃):CH (R₁₃ = H, alkyl, Ph); R₁, R₂ = H, alkyl, alkoxyalkyl, aralkyl; R₁R₂N = (substituted) (ring-fused) heterocyclyl; R₃, R₄ = H, OH, alkyl, alkoxy, points of attachment of a spiro 5- or 6-membered heterocyclic ring containing 1 O or S atom; A = alkyl, carbocyclyl, (substituted) Ph, naphthyl, etc.], were prepared. Thus, benzo[b]thiophene-4-acetic acid was converted to the acid chloride, which reacted with trans-2-(4-morpholinyl)cyclohexanol in CHCl₃ to give trans-2-(4-morpholinyl)cyclohexyl benzo[b]thiophene-4-acetate, isolated as the hydrochloride. The latter at 8 μmoles/kg/min in rats gave an arrhythmia score of 0.3, vs 7 for vehicle only.

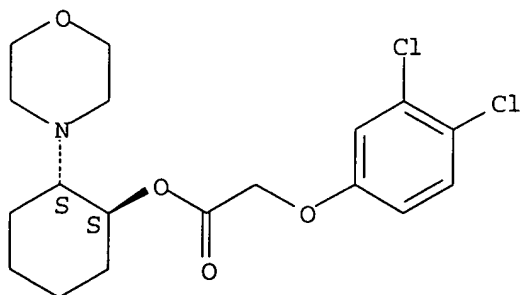
IT **169191-23-5P 169191-37-1P 169191-52-0P**
192446-66-5P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of 2-heterocyclylcyclohexyl esters as antiarrhythmics)

RN 169191-23-5 CAPLUS

CN Acetic acid, (3,4-dichlorophenoxy)-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



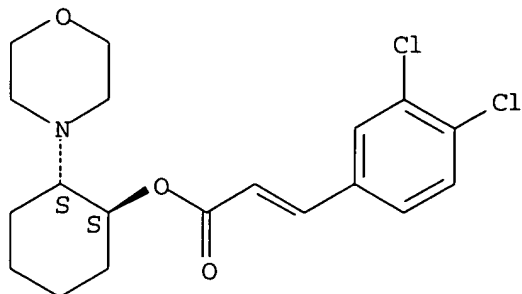
● HCl

RN 169191-37-1 CAPLUS

CN 2-Propenoic acid, 3-(3,4-dichlorophenyl)-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.

Double bond geometry unknown.

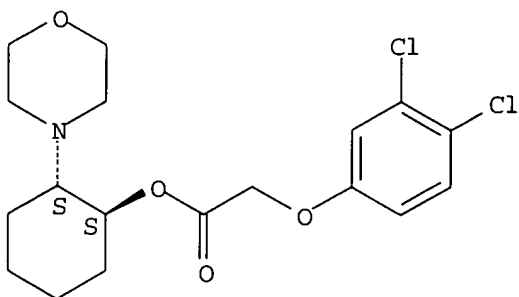


● HCl

RN 169191-52-0 CAPLUS

CN Acetic acid, (3,4-dichlorophenoxy)-, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

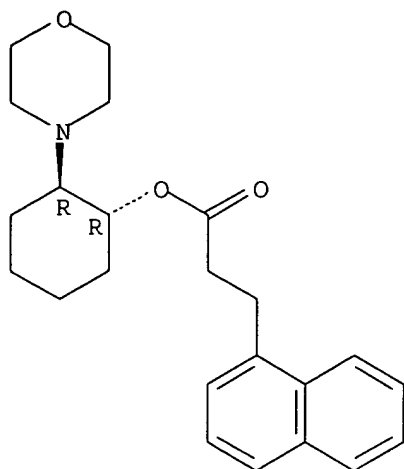
Relative stereochemistry.



RN 192446-66-5 CAPLUS

CN 1-Naphthalenepropanoic acid, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L11 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1995:867587 CAPLUS

DOCUMENT NUMBER: 123:286082

TITLE: Preparation of heterocyclohexyl esters as antiarrhythmics

INVENTOR(S): MacLeod, Bernard A.; Walker, Michael J. A.; Wall, Richard A.

PATENT ASSIGNEE(S): University of British Columbia, Can.

SOURCE: PCT Int. Appl., 91 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

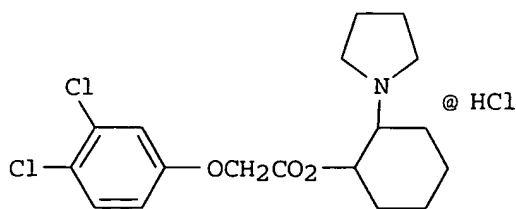
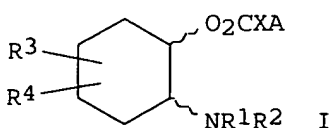
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9508544	A1	19950330	WO 1994-CA513	19940923
W: AU, BR, CA, CN, CZ, FI, HU, JP, KR, NO, NZ, PL, RU, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2172513	AA	19950330	CA 1994-2172513	19940923
AU 9476502	A1	19950410	AU 1994-76502	19940923
EP 720605	A1	19960710	EP 1994-926755	19940923
EP 720605	B1	20011219		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
AT 211135	E	20020115	AT 1994-926755	19940923
ES 2170102	T3	20020801	ES 1994-926755	19940923
PRIORITY APPLN. INFO.:			US 1993-126575	A 19930924
			WO 1994-CA513	W 19940923

OTHER SOURCE(S): MARPAT 123:286082

GI



II

AB Title compds. I (X = bond, (CH₂)_nY, CH(R₁₂)Y, CR₁₃:CH wherein n = 1-3, Y = bond, O, S, R₁₂ = C1-6 alkyl, C3-6 carbocyclyl, Ph, PhCH₂, R₁₃ = H, C1-6 alkyl, Ph; R₁, R₂ =H, C3-8 alkyl, C3-8 alkoxyalkyl, C7-12 aralkyl; R₁R₂ = (substituted)heterocyclyl; R₃, R₄ = H, HO, C1-6 alkyl, C1-6 alkoxy, etc.; A = C5-12 alkyl, (substituted)Ph, etc.), a solvate or salt thereof, are prepared I are also useful as ion e.g., Na channel blockers. Pyrrolidine, cyclohexene oxide and water were reacted to give (±)-trans-[2(1-pyrrolidinyl)]cyclohexanol to which was added 3,4-dichlorophenoxyacetyl chloride to give the title compound (±)-trans-II. Antiarrhythmic and Na channel blocking activity were demonstrated.

IT 169191-23-5P 169191-37-1P 169191-39-3P

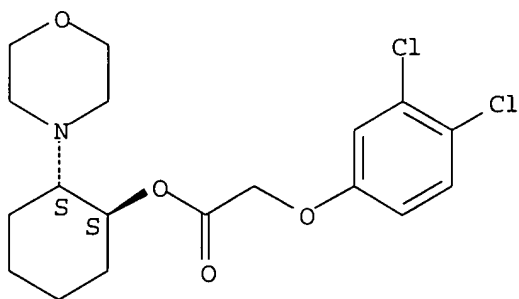
169191-52-0P 169191-66-6P 169191-68-8P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of heterocyclohexyl esters as antiarrhythmics)

RN 169191-23-5 CAPLUS

CN Acetic acid, (3,4-dichlorophenoxy)-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



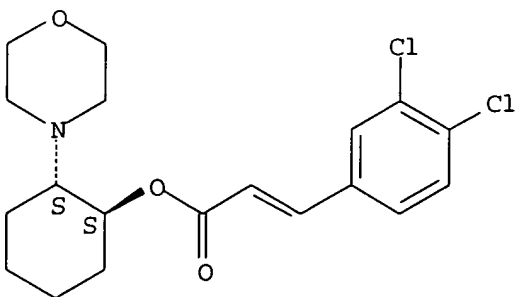
● HCl

RN 169191-37-1 CAPLUS

CN 2-Propenoic acid, 3-(3,4-dichlorophenyl)-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.

Double bond geometry unknown.

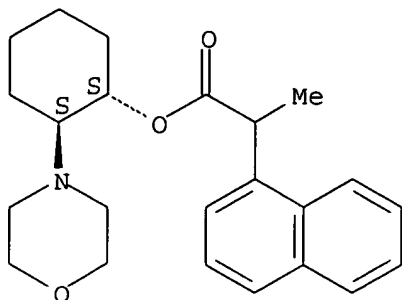


● HCl

RN 169191-39-3 CAPLUS

CN 1-Naphthaleneacetic acid, α -methyl-, 2-(4-morpholinyl)cyclohexyl ester, hydrochloride, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.

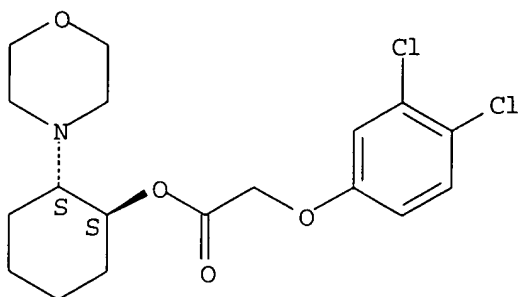


● HCl

RN 169191-52-0 CAPLUS

CN Acetic acid, (3,4-dichlorophenoxy)-, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

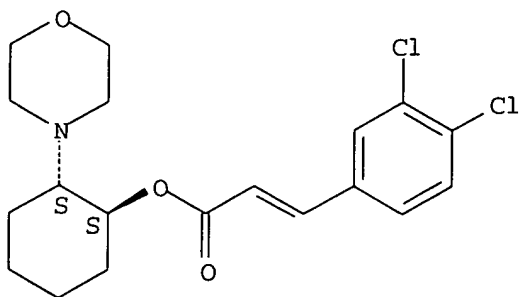
Relative stereochemistry.



RN 169191-66-6 CAPLUS

CN 2-Propenoic acid, 3-(3,4-dichlorophenyl)-, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

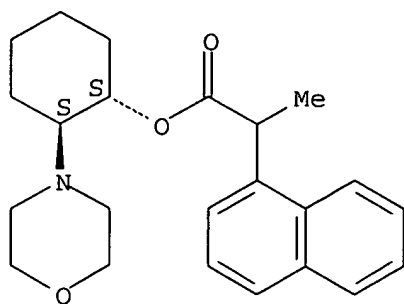
Relative stereochemistry.
Double bond geometry unknown.



RN 169191-68-8 CAPLUS

CN 1-Naphthaleneacetic acid, α -methyl-, 2-(4-morpholinyl)cyclohexyl ester, trans- (9CI) (CA INDEX NAME)

Relative stereochemistry.



L11 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN

ACCESSION NUMBER: 1959:39941 CAPLUS

DOCUMENT NUMBER: 53:39941

ORIGINAL REFERENCE NO.: 53:7177i,7178a-i,7179a-i,7180a-i,7181a

TITLE: Mechanism of chemical reactions. XVIII. Specific catalytic condensations with dihalides. 1. Conversion of aliphatic-aromatic dichlorides into amines with properties of local anesthetics

AUTHOR(S): Kindler, Karl; Hansen, Werner; Koebke, Jurgen

CORPORATE SOURCE: Univ. Hamburg, Germany

SOURCE: Ann. (1958), 617, 25-54

DOCUMENT TYPE: Journal

LANGUAGE: Unavailable

OTHER SOURCE(S): CASREACT 53:39941

AB cf. C.A. 52, 9015g. PhCH₂CH₂OH (980 g.) at 130° was treated dropwise with 1 kg. SOCl₂, heated another 1.5 hrs., giving 1.012 kg. PhCH₂CH₂Cl, b₁₀ 78-9°, 5 moles of which with 75 g. paraformaldehyde and 75 g. anhydrous ZnCl₂, stirred 30 min. at 45°, treated 6.5 hrs. with a rapid stream of HCl (keeping a slight pressure for 30 min.), washed repeatedly with saturated aqueous NaCl, and then with aqueous NaCl and NaHCO₃

to

insure complete removal of HCl and ZnCl₂, and fractionated gave 337 g. 4-ClCH₂CH₂C₆H₄CH₂Cl (I), b₉ 137-8°, m. 34-5° (MeOH-PrOH with traces H₂O). Similarly, 8.4 moles SOCl₂ and 8 moles Ph(CH₂)₃OH gave 1.1 kg. Ph(CH₂)₃Cl, b₈ 86-88°, 775 g. of which with 75 g. paraformaldehyde gave 345 g. 4-Cl(CH₂)₃C₆H₄CH₂Cl (II), b₉ 150-2°, n_D²⁰ 1.5468. I with excess morpholine (III) in xylene, heated 14 hrs. at 125° gave p-(RCH₂CH₂)C₆H₄CH₂R (R = morpholino), b_{0.8} 184-6°; dipicrate, m. 190-2°. Similarly III and II gave p-RCH₂CH₂CH₂C₆H₄CH₂R, b_{0.9} 196-8°; dipicrate, m. 202-3°. These derivs. of III were used in judging the purity of various preps. of I and II. Mesitylene (IV) and other aromatic hydrocarbons and ethers (in excess) were condensed with I or II by using min. amts. of FeCl₂ as catalyst, and passing CO₂-free air through the mixture to remove HCl. Excessive amts. of FeCl₃ gave greatly decreased yields. The following monochlorides, p-R'CH₂C₆H₄CH₂CH₂Cl (V) were obtained from 0.1 mole I (other reactant, mg. FeCl₃, temperature, reaction time in min. R', b.p./mm.,

and

% yield of V given): C₆H₆, 90, 90°, 80, Ph, 185-7°/8, 59; IV, 0.06, 115°, 45, 2,4,6-MeC₆H₂, 207-9°/8, 78; MeOPh, 60, 110°, 60, 4-(MeO)C₆H₄, 212-15°/10, 84; 2-MeC₆H₄OMe, 15, 115°, 15, 3,4-Me(MeO)C₆H₃, 229-33°/16, 76; 2-ClC₆H₄OMe, 30, 115°, 35, 3,4-Cl(MeO)C₆H₃, 215-17°/0.7, 58. Similarly formed from II were the following p-R'CH₂C₆H₄CH₂CH₂Cl (VI) (with similar data given): naphthalene, 67, 100°, 25, α-Cl₁₀H₇, 221-23°/1.5, 59; 1-methylnaphthalene, 81, 100°, 20, 4-MeCl₁₀H₆, 232-4°/1.1, 68; Tetralin, 50, 120°, 100,

5,6,7,8-tetrahydro- β -naphthyl, 214-16°/1.4, 58; IV, 0.17, 115°, 25, 2,4,6-Me₃C₆H₂, 196-99°/1.3, 79; PhMe, 30, 100°, 30, 4-MeC₆H₄, 205-8°/10, 60; PhEt, 30, 110°, 40, 4-EtC₆H₄, 214-17°/10, 73; PhPr, 15, 115°, 60, 4-PrC₆H₄, 180-1°/0.8, 66; 1,4-Me₂C₆H₄, 30, 110°, 20, 2,5-Me₂C₆H₃, 214-18°/10, 70; 1,2-Me₂C₆H₄, 90, 110°, 90, 3,4-Me₂C₆H₃, 220-23°/10, 73; 4-iso-PrC₆H₄, 45, 155-60°, 70, 2,5-Me(iso-Pr)C₆H₃, 186-90°/0.8, 70; PhCl, 15, 115°, 35, 4-ClC₆H₄, 174-77°/0.8, 22; p-ClC₆H₄OH, 4, 100°, 85, 5,2-Cl(HO)C₆H₃, 226-30°/1.2, 57; o-ClC₆H₄OH, 5, 100°, 3,4-Cl(HO)C₆H₃, 90, 232-36°/1.1, 63; MeOPh, 11, 100° 35, 4MeOC₆H₄, 185°/1.5, 68; EtOPh, 24, 100°, 30, 4-EtOC₆H₄, 208-10°/2.4, 65; PrOPh, 25, 100°, 65, 4-PrOC₆H₄, 214-18°/2.2, 69; BuOPh, 10, 100°, 25, 4-BuOC₆H₄, 207-10°/1.2, 59; 2-ClC₆H₄OMe, 6, 100°, 20, 3,4-Cl-(MeO)C₆H₃, 213°/1.3, 73; 2-ClC₆H₄OEt, 7, 100°, 40, 3,4-Cl(EtO)C₆H₃, 225-27°/2, 66; 2-ClC₆H₄OPr, 18, 130°, 25, 3,4-Cl(PrO)C₆H₃, 219-21°/0.8, 66; 2-iso-PrC₆H₄Cl, 17, 130°, 30, 3,4-Cl(iso-Pr)C₆H₃, 204-6°/0.9, 52; 2-ClC₆H₄Bu 18, 125°, 15, 3,4-Cl(Bu)C₆H₃, 238-40°/1.3, 64; 2-Me-C₆H₄OMe, 6, 100°, 120, 3,4-Me(MeO)C₆H₃, 200-3°/1.5, 72; 4-MeC₆H₄OMe (VII), 23, 110°, 130, 5,2-Me(MeO)C₆H₃ (VIIa), 204-6°/2.6, 62; 2-MeC₆H₄OEt, 15, 100°, 30, 3,4-Me(EtO)C₆H₃, 201-3°/0.9, 75; 2-MeC₆H₄OPr, 16, 125°, 30, 3,4-Me(PrO)C₆H₃, 207-9°/1.3, 66; 2-MeC₆H₄OBu, 28, 145°, 65, 3,4-Me(BuO)C₆H₃, 217-19°/1.6, 63; 2-MeC₆H₄OCH₂CH₂OEt, 66, 120°, 170, 3,4-Me(EtOCH₂CH₂)C₆H₃, 225-32°/1.5, 78; Ph₂O, 12, 105°, 140, 4-PhOC₆H₄, 225-7°/0.7, 65; 1,2(MeO)₂C₆H₄, 25, 120°, 25, 3,4-(MeO)₂C₆H₃, 212-14°/1, 62; 1,3-(MeO)₂C₆H₄, 11, 110°, 215, 2,4-(MeO)₂C₆H₃, 235-7°/4, 74; 1,2,3(MeO)₂C₆H₃, 18, 130°, 15, 2,3,4-(MeO)₃C₆H₂, 229-31°/1.5, 69; 1-MeO-C₁₀H₇, 9, 100°, 20, 4-MeOC₁₀H₆, 243-6°/1.3, 68; dihydrosafrole 30, 100°, 50, 3,4-(CH₂O₂)-6-PrC₆H₂, 214-19°/0.8, 62; dihydroeugenol Me ether, 30, 110°, 65, 3,4,6(MeO)₂PrC₆H₂, 205-8°/0.4, 69; dihydroanethole, 30, 110°, 35, 2,5-(MeO)PrC₆H₃, 191-4°/0.6, 61. In forming the following VI, from 0.15-0.2 mole II, anhydrous AlCl₃ or ZnCl₂ was used (reactant, mg. of catalyst, temperature and reaction period in min, R', b.p./ mm. and yield given): C₆H₆, 105 AlCl₃, 90°, 120, Ph, 191-2°/6, 42; PhF, 193 AlCl₃, 90°, 200, 4-FC₆H₄, 180-3°/3, 25; PhCl, 147 AlCl₃, 105°, 60, 4-ClC₆H₄, 203-4°/2.7, 20; PhBr, 118 AlCl₃, 110°, 60, 4-BrC₆H₄, 218-20°/3.5, 17; VII, 42 AlCl₃, 110°, 90, VIIa, 198-200°/2.6, 83; Ph₂O 9 AlCl₃, 105°, 80, 4-PhOC₆H₄, 247-9°/2, 63; MeOPh, 12 ZnCl₂, 100°, 70, 4-MeOC₆H₄, 209-11°/2.6, 70; VII, 32 ZnCl₂, 110°, 35, VIIa, 198-200°/2.6, 74. V and VI were purified by repeated distns.; no analyses are given. V and VI were condensed with primary or secondary amines in Et₃N or xylene, usually by heating 16-20 hrs. at 125°, using sealed tubes when required. After removal of the solvent and excess amine, the products were frequently extracted with Et₂O converted into the HCl salts, which after washing with Et₂O were reconverted into the free bases and extracted with Et₂O. The exts. were washed with H₂O and recoveries were obtained both from the Et₂O exts. and H₂O-washings. From V the products were p-RCH₂C₆H₄CH₂CH₂R'' (VIII) (R'' = substituted amino group). V (R = Ph) with MeNH₂ in Et₃N gave 79% VIII (R = Ph, R'' = NHMe), b1 149-51; HCl salt, m. 191-2°: picrate, m. 95-6°. Similarly formed from the appropriate V and III in xylene were 92% VIII (R = 4-MeOC₆H₄, R'' = morpholino), b1 218-20°, and 89% VIII (R = 2,4,6-Me₃C₆H₂; R' = morpholino), b14 220-2°, n₂₀D 1.5634. Similarly from the appropriate V and amine were formed 63% VIII (R = 3,4-Me(MeO)C₆H₃, R'' = Et₂N), b0.3 175-8°, n₂₀D 1.5458, and 76% VIII (R = 3,4-Cl(MeO)C₆H₃, R'' = morpholino), b2 242-6°. Analogous condensation, usually under similar conditions, were effected with the appropriate VI and various amines giving the following compds. p-R'CH₂C₆H₄CH₂CH₂R'' (IX) (R',

R'' , b.p./mm. % yield and n_{20D} given): α -ClO₁₀H₇, morpholino, 252-4°/1.8, 89, -; 4-MeClO₁₀H₆, morpholino, 260-2°/0.8, 92, -; 5,6,7,8-tetrahydro- β -naphthyl, morpholino, 243-6°/1.6, 94, -; tetrahydro- β -naphthyl, Et₂N, 208-11°/0.6, 77, 1.5569; 2,4,6-Me₃C₆H₂, morpholino, 233-5°/1.7, 92, -; 4-MeC₆H₄, morpholino, 193-5°/0.4, 82, 1.5582; 4-MeC₆H₄, Et₂N, 173-5°/0.6, 73, 1.5401; 4-EtC₆H₄, morpholino, 203-6°/0.5, 83, 1.5548; 4-EtC₆H₄, Et₂N, 175-8°/0.5, 72, 1.5381; 4-PrC₆H₄, Et₂N, 194-7°/0.9, 65, 1.5338; 4-PrC₆H₄, morpholino, 216-19°/0.9, 72, 1.5504; 2,5-Me₂C₆H₃, morpholino, 208-11°/0.5, 88, 1.5581; 2,5-Me₂C₆H₃, Et₂N, 174-7°/0.5, 71, 1.5407; 3,4-Me₂C₆H₃, morpholino, 204-7°/0.4, 84, 1.5589; 3,4-Me₂C₆H₃, Et₂N, 181-4°/0.6, 67, 1.5417; 2,5-Me(iso-Pr)C₆H₃, morpholino, 243-5°/1.7, 83, -; 4-ClC₆H₄, Et₂N, 190-2°/0.6, 1.5493; 5,2-Cl(HO)C₆H₃, morpholino, 270-1°/2.5 (with subsequent crystallization), 85, -; 3,4-Cl(HO)C₆H₃, morpholino, 260-4°/0.7 (with crystallization), 81, -; 4-MeOC₆H₄, morpholino, 239-40°/3, 92, -; 4-MeOC₆H₄, N-cyclohexyl methylamino, 242-4°/2, 78, -; 4-MeOC₆H₄, (CH₂:CHCH₂)₂N, 232°/0.5, 78, -; 4-MeOC₆H₄, Pr₂N, 213-15°/1.3, 60, -; 4-MeOC₆H₄, pyrrolidino, 206-8°/1, 93°, -; 4-EtOC₆H₄, morpholino, 232-4°/1.2, 89, -; 4-PrOC₆H₄, morpholino, 235-7°/1, 87, -; 4-BuOC₆H₄, morpholino, 254-6°/1.7, 88, -; 3,4-Cl(MeO)C₆H₃, morpholino, 242°/1.2, 86, -; 3,4-Cl(MeO)C₆H₃, MeNBu, 226-8°/1, 50, -; 3,4-Cl(EtO)C₆H₃, morpholino, 3,4-Cl(PrO)C₆H₃, morpholino, 250-2°/1.1, 87, -; 3,4-Cl(iso-PrO)C₆H₃, morpholino, 249-51°/1.4, 54, -; 3,4-Cl(BuO)C₆H₃, morpholino, 246-8°/1, 87, -; 3,4-Me(MeO)C₆H₃, morpholino, 226-8°/1, 89, -; in the following VIII. R = 3,4-Me(MeO)C₆H₄, and only R'' , b.p./mm. and % yields are given: Et₂N, 208°/0.4, 68, EtBuN, 206-9°/0.5, 76; Bu₂N, 244-7°/0.7, 57; (CH₂:CHCH₂)₂N, 230-2°/0.6, 80; 2-methyl-1-piperidyl, 229-32°/1, 83; 2,5-dimethyl-1-piperazinyl, 239-42°/1, 41. In the following VIII, R and R'' b.p./mm. and yields are given: 5,2-Me(MeO)C₆H₃, morpholino, 234-7°/1.1, 85; 3,4-Me(EtO), C₆H₃, morpholino, 221-23°/0.7, 91; 3,4-Me(EtO)C₆H₃, Et₂N, 193-7°/0.6, 84, n_{20D} 1.5362; 3,4-Me(PrO)C₆H₃, morpholino, 247-9°/1.3, 86; 3,4-Me(PrO)C₆H₃ Et₂N, 195-8°, 67, n_{20D} 1.5323; 3,4-Me(BuO)C₆H₃, morpholino, 244-6°/1.5, 93; 3,4-Me(EtOCH₂CH₂)C₆H₃, morpholino, 253-7°/1.2, 75; 4-PhOC₆H₄, morpholino, 263-5°/1.1, 87; 3,4-(MeO)₂C₆H₃, morpholino, 232-4°/0.6, 88; 2,4-(MeO)₂C₆H₃, morpholino, 232-3°/0.8, 89; 2,3,4-(MeO)₃C₆H₂, morpholino, 246-7°/1.5, 87; 4-MeOC₁₀H₆, morpholino, 268-70°/0.8, 85; 3,4-(CH₂O₂)₆-PrC₆H₂, morpholino, 242-4°/0.6, 61, n_{20D} 1.5601; 3,4-(CH₂O₂)₆-PrC₆H₂, Et₂N, 206-9°/0.5, 62, n_{20D} 1.5451; 3,4,6-(MeO)₂PrC₆H₂, morpholino, 245-7°/0.7, 86, n_{20D} 1.5538; 3,4,6-(MeO)₂PrC₆H₂, Et₂N, 209-12°/0.6, 78, n_{20D} 1.5382; 2,5-(MeO)PrC₆H₃, morpholino, 230-2°/0.6, 87, n_{20D} 1.5510; 2,5-(MeO)PrC₆H₃, Et₂N, 190-2°/0.4, 71, n_{20D} 1.5357; 3,4-Me(MeO)C₆H₃, MeOCH₂CH₂CH₂NH, 219-22°/0.7, 84, n_{20D} 1.5450. Na (0.1 g. atom) powdered by heating in 40 cc. boiling xylene was treated with a suitable amino alc. (usually β -morpholinoethanol (IX) in 10 cc. xylene, and heated 15 hrs. at 150° with the appropriate VI. The mixture was treated with Et₂O and the organic phase washed with H₂O, shaken with 6% HCl, and the resulting salt reconverted into the free ether with KOH, extracted with Et₂O, washed and distilled to give the following p-derivs. of γ -phenylpropyl β -morpholinoethyl ether (p-substituent, b.p./mm., and % yield given): α -naphthylmethyl, 272°/1, 72; 4-FC₆H₄CH₂, 236-9°/1.8, 81; 4-MeOC₆H₄CH₂, 242-4°/0.8, 82; 3,4-Cl(PrO)C₆H₃CH₂, 284-6°/2, 79; 3,4-Cl(BuO)C₆H₃CH₂, 276-82°/1.0-1.3, 77; 3,4-Me(MeO)C₆H₃CH₂, 258-60°/1.5, 85; 3,4-Me(EtO)C₆H₃CH₂, 253-6°/0.9, 70; 3,4-Me(PrO)C₆H₃CH₂, 262-4°/1.5, 67; 3,4-Me(EtOCH₂CH₂)C₆H₃CH₂, 274-7°/1.5, 61; PhOC₆H₄CH₂, 297-99°/0.7, 72; 2,4-(MeO)₂C₆H₃CH₂, 262-4°/1.0, 60. Formed analogously were the following [p-(4-methoxybenzyl)- γ -phenylpropyl]-

β -piperidinoethyl ether, 227-9°/0.7, 75; [p-(4-methoxy-3-methylbenzyl)- γ -phenylpropyl]- β -dibutylaminoethyl ether, 279-82°/1.1, 53; and [p-(2-methoxy-5-methylbenzyl)- γ -phenylpropyl]-2-morpholinocyclohexyl ether, 276-9°/1.3, 40. 2-O₂NC₆H₄OMe (X) (0.6 mole) heated 90 min. at 115° with 0.2 mole 4-[Cl(CH₂)₃]C₆H₄CH₂Cl and 90 mg. FeCl₃ gave p-(4-methoxy-3-nitrobenzyl)- γ -phenylpropyl chloride (XI) which could not be distd; after removing excess X, 67 g. crude XI was treated with 52.3 g. III to give 49 g. crude, undistillable N-[(p-4-methoxy-3-nitrobenzyl)- γ -phenyl]morpholine, (XII), 18.5 g. of which, in 150 cc. MeOH was hydrogenated 8 hrs. with 10 g. moist Raney Ni at 2.5 atmospheric, filtered, treated with 6%

HCl,

and processed as above, to yield 53% 3-NH₂ analog of XII, C₂₁H₂₈N₂O₂, b_{0.7} 250-3°/1, m. 67-8°. p-[5,2-Me(MeO)C₆H₃CH₂]C₆H₄(CH₂)₃Cl (XIII) (0.2 mole), heated and stirred 22 hrs. with 0.24 mole NaI in 200 cc. PrOH, evaporated, treated with H₂O and the resulting crude iodide analog (XIIIa) of XIII was filtered; the aqueous solution was extracted repeatedly

with

Et₂O, and these evaporated exts. were combined with XIIIa, b₁₂ 212-28° (total yield 78%). XIIIa (53.8 g.) with 18.2 g. KCN in 250 cc. 80% PrOH, stirred and refluxed 20 hrs., evaporated, dissolved in H₂O and extracted with

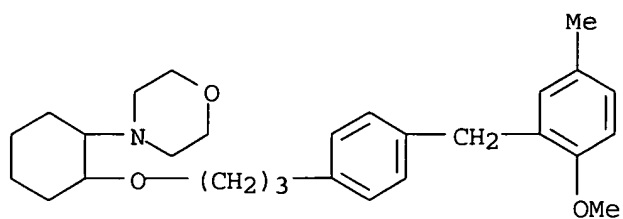
Et₂O

gave 33.2 g. crude p-(2-methoxy-5-methylbenzyl)- γ -phenylbutyrylonitrile (XIV), freed from residual XIIIa by heating with III in xylene and extracting with 6% HCl. Purified XIV, b_{1.5} 202-9°. XIV (9.3 g.) hydrogenated and shaken with 20 g. moist Raney Ni in MeOH saturated with NH₃, filtered, evaporated dissolved in dilute HCl, washed with Et₂O, and made alkaline with KOH gave 5 g. p-(5,2-Me(MeO)C₆H₃CH₂C₆H₄(CH₂)₄NH₂, (XV), b_{0.8} 194-7°. Formed analogously to XV with only slight modifications from the appropriate nitrile was p-(3,4-Me(MeO)C₆H₃CH₂)C₆H₄(CH₂)₄NH₂, very hygroscopic, b₁ 208-11°. A mixture of 14 g. p-(3,4-Me(MeO)C₆H₃CH₂)C₆H₄(CH₂)₃CN, 13 g. III and 50 cc. MeOH was hydrogenated at 20° with Raney Ni as above to give 6.9 g. crude N-[p-(3-methyl-4-methoxybenzyl)- δ -phenylbutyl]morpholine (XVI), purified by treating in Et₂O with BzCl and aqueous NaOH, separating the

Et₂O

phase, treating with dilute HCl, and freeing the base with KOH to give 5.0 g. XVI, b_{1.5} 242-5°; picrolonate, m. 210°. PhCH₂Cl (0.1 mole) and 0.6 mole MeOPh (XVII) or 2-MeC₆H₄OMe and small amts. of FeCl₃ reacted readily at 100° giving the usual type of condensation products (e.g. PhCH₂C₆H₄Me) in yields of 80-87%; with large amts. of FeCl₃ yields decreased, and in the absence of catalyst no condensations occurred. Mesitylene reacted readily with 0.1 mole p-MeOC₆H₄CH₂Cl and 0.012 mg. FeCl₃. Ph(CH₂)₂Cl or Ph(CH₂)₃Cl, even in the presence of small amts. of FeCl₃ failed to react with XVII. With large amts. of FeCl₃, at 150°, HCl was liberated, but no identifiable products were isolated. In the presence of 0.0005 mole of certain inhibitors (notably substituted thiobenzamides and (Et₂N)₂CO), the yields of PhCH₂C₆H₄OMe were decreased greatly, unless much larger amts. of FeCl₃ were used. E.g. in the presence of 0.0005 mole N-thiobenzoylpiperidine (XVIII), the amount of FeCl₃ had to be increased from the usual 1 mg. to 81 mg. to give a satisfactory yield of PhCH₂C₆H₄OMe. Whereas 0.3 mole XVII, 0.1 mole PhCH₂Cl, and 1 mg. FeCl₃ at 115° gave 70% PhCH₂C₆H₄OMe in 30 min., the introduction initially of 0.1 g. XVIII gave rise to neither HCl nor PhCH₂C₆H₄OMe. Neither diethyl- nor phenylethylbarbituric acid served as inhibitors. PhCH₂Cl (25.4 g.) and 60 mg. FeCl₃ in PhNO₂ reacted violently giving HCl and a resin, however, when 0.5 g. Me(CH₂)₄CONH₂ or Me(CH₂)₁₆CONH₂ was added to the original mixture no HCl was formed, even on heating several hrs., and PhCH₂Cl was recovered almost quantitatively. Similar results were obtained when these amides were added to other arylmethyl chlorides, I, or II, even in the presence of such resin-forming catalysts as ZnCl₂ or AlCl₃. The statement is made that the above condensations (giving amines) can yield local anesthetics; no pharmacol. data are given.

IT 104397-47-9, Morpholine, 4-[2-[3-[α-(6-methoxy-m-tolyl)-p-
tolyl]propoxy]cyclohexyl]-
(preparation of)
RN 104397-47-9 CAPLUS
CN Morpholine, 4-[2-[3-[α-(6-methoxy-m-tolyl)-p-
tolyl]propoxy]cyclohexyl]- (6CI) (CA INDEX NAME)



=> log y

COST IN U.S. DOLLARS

SINCE FILE
ENTRY

TOTAL
SESSION

FULL ESTIMATED COST

30.09

283.19

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE
ENTRY

TOTAL
SESSION

CA SUBSCRIBER PRICE

-4.38

-4.38

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